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EXPERIMENTAL STUDIES ON CHRONIC POISONING OF RABBITS WITH LOW CONCENTRATIONS OF CHLORINE AND THE DEVELOPMENT OF THE OFFSPRING OF THE CHLORINE-POISONED RABBITS

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EXPERIMENTAL STUDIES ON CHRONIC POISONING OF RABBITS WITH LOW CONCENTRATIONS OF CHLORINE AND THE DEVELOPMENT OF THE OFFSPRING OF THE CHLORINE-POISONED RABBITS

[Experimentelle Studien uber chronische Vergiftung von Kaninchen mit geringen Chlorkonzentrationen und die Entwicklung der Nachkommenschaft der chlorvergifteten Kaninchen]

R.M. Skljanskaja, L.M. Klaus and L.M. Ssidorowa

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EXPERIMENTAL STUDIES ON CHRONIC POISONING OF RABBITS WITH LOW CONCENTRATIONS OF CHLORINE AND THE DEVELOPMENT OF THE OFFSPRING OF THE CHLORINE-POISONED RABBITS

by

R. M. Skljanskaja and J. L. Rappoport

During our studies on the effect of chlorine on the female organism, we realized that the problem of the chronic effect of chlorine has had very little experimental work [1 - 25]. We find even fewer statements on the possible effect of chronic chlorine toxicity on the course of pregnancy (or the health of the offspring). The last problem is of special importance in view of the fact that women also work in chlorine plants. To supplement our clinical investigation, then, we undertook a further experimental study of the chronic intoxication of rabbits with very low chlorine concentrations.

We set up the following objectives:

1. We would clarify, by histopathological studies, the chronic effect of the very slight chlorine concentrations similar to those occurring under working conditions; and
2. We would study the offspring of rabbits chronically poisoned with small amounts of chlorine.

The experiments were done in a specially made chamber which could be hermetically sealed (see Figure 1). It had a capacity of some 470 liters. Four rabbits could be treated simultaneously in this chamber. The walls are of glass, and the top and bottom of wood. There are three openings in the walls: for the introduction of chlorine, for air exchange, and at the same time for aspiration of gas (to determine the chlorine concentration in the chamber, and

for the removal of urine (bottom). The chlorine was obtained by the action of hydrochloric acid on manganese dioxide of potassium permanganate (1:1). The gas was collected and held in a gasometer over concentrated sodium chloride solution.

The chlorine was introduced into the chamber in the following way. The gasometer, full of chlorine, was connected through a bent glass tube to a gas buret provided with two stopcocks and a water-filled levelling vessel. The gas buret was connected to the chamber, into which chlorine flowed at a rate of 2 cm^3 per minute. The gas was regulated by the lower stopcock of the buret.

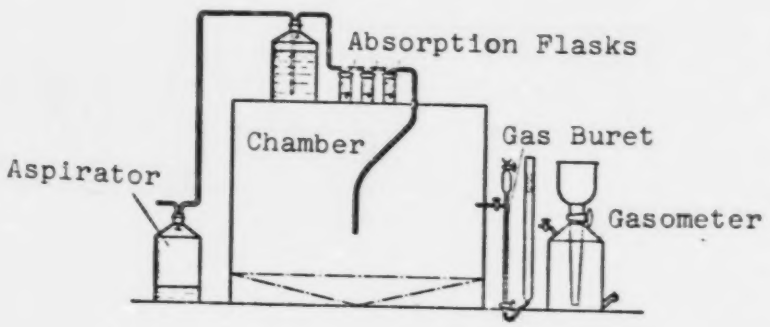

Figure 1. Setup for experimental investigation of the chronic effect of low chlorine concentrations on rabbits.

In the chamber, at the breathing level of the experimental animals, a glass tube was placed, through which the chlorine, mixed with air, left the chamber. Through a three-way stopcock, the chlorine from the chamber passed simultaneously into a Petri absorption vessel filled with 10 cm^3 N/500 As_3O_3 solution and into a porcelain bottle with a flowmeter, connected to a three-necked bottle. The latter was connected to two water jet aspirators for air exchange.

Chlorine was determined by absorption in a N/500 As_2O_3 solution. Four samples were taken each day. The reaction proceeded according to the following equation:

$$As_2O_3 + 2\,Cl_2 + 2\,H_2O = As_2O_5 + 4\,HCl$$

After the end of the aspiration, the solution from the absorption vessel was poured into a flask, mixed with 2% starch solution, and titrated with N/500 iodine solution. The difference between the amount of iodine solution in the first and second titrations gave the number of cubic centimeters of iodine solution which corresponded to the absorbed chlorine. In both cases, the starch content of the solution to be titrated must be approximately the same.

The calculation was done by the following system: 400 cm^3 of As_2O_3 required a cm^3 iodine solution before the experiment. After the experiment, the same amount required a_1 cm^3 iodine solution, and e liters of air were sampled.

$0.0709\ (a_1 - a)/e$ corresponds to the number of milligrams of chlorine in one liter of air.

During 5 hours of exposure, the concentrations varied between 0.002 and 0.005 mg Cl_2 per liter of air.

During the poisoning experiments, there were always 4 rabbits in the chamber at the same time. Two parallel groups of 4 rabbits each were subjected to the action of chlorine. Each group received its portion of chlorine every other day, for 5 hours without interruption. One group of rabbits was exposed in this way from April 1932 to January, May and October, 1933. A second part of the rabbits was treated from October 1932 until May 1933. The duration of chronic poisoning varied between one and nine months. The number of individual experiments was between 11 and 119.

The experiments were done at concentrations of 0.002 to 0.005 mg Cl_2 per liter of air, inasmuch as these concentrations can be regarded as approximately the industrial concentrations and, according to literature statements, as the threshold values for effective concentrations. It must be emphasized that their

effect in long-term chronic exposure is still completely unstudied experimentally.

After the fourth month of exposure, the experimental animals were mated. In a series of rabbits, pregnancy occurred only after the second, third, or fourth mating. In many individuals it did not occur at all in spite of repeated matings (from two to eight times). Part of the rabbits died before mating. During pregnancy, exposure was continued almost to delivery. Many times there was an interruption of some 3 - 4 days before delivery. The exposures were started again at 3 weeks after delivery and continued for another 1 - 2 months. After the end of the intoxication, we observed the experimental animals frequently for several more months. Part of the rabbits died some months after the end of the poisoning. Part of them were killed by cutting the carotid artery or by electricity after a long period of observation after the completion of poisoning.

The nutritional regime of all the experimental animals was qualitatively and quantitatively satisfactory throughout the year except for the summer months. It consisted of hay, oats and sugar beets. From mid-May to mid-August the food consisted of grass, hay, and oats. The body weights of the rabbits were determined systematically. There were 16 experimental animals, of which one rabbit served as the control and 15 were subjected to chronic chlorine poisoning.

Our data can be summarized as follows: From Table 1 we see that 11 rabbits (No. 1, 2, 3, 4, 5, 6, 7, 8, 9, 18, 19) which were exposed from 11 to 119 times, died, while 4 rabbits (No. 15, 17, 21, 22) which were exposed from 71 to 84 times, were only killed later.

Four rabbits died even before mating (No. 1, 5, 8, 19); i. e., after three months of poisoning. Four rabbits (No. 7, 18, 4, 6) were not impregnated in spite of repeated matings (from 2 to 8 times). Nine rabbits did not give birth, but autopsy showed a macerated fetus in the abdomen. Six rabbits gave birth (No. 2, 3, 15, 17, 21, 22), of which female No. 3 gave birth twice. In female No. 21

macerated fetuses were demonstrated in the abdomen on autopsy, (26) in spite of the birth of young.

In four rabbits, (No. 15, 21, 22, 17), gravidity occurred after the first mating in the fifth month of poisoning (after 49 - 54 experiments). For rabbit No. 2, it occurred after the first mating in the fourth month of poisoning (after 32 experiments). For rabbit No. 3 it occurred only after the second mating in the fourth month of poisoning (after 37 experiments), and, for the second time, after a third mating in the third month of poisoning (after 26 experiments).

For the poisoned rabbits, we observed weight losses in the range of 2.5 - 43.6% (Table 1). The degree of weight loss did not parallel the duration of poisoning. Rabbits No. 4, 15, 6, 17, 21, and 22 showed less weight loss after 68 - 84 poisonings than rabbits No. 8, 19, 5, and 1, which were much less exposed to the toxic effect.

Toward the end of the intoxication experiment the weight loss was often significantly less than toward the end of the whole observation, i. e., 1 - 2 months after the end of exposure. For instance, rabbit No. 4 showed a weight loss of 13.9% at the end of exposure, but a loss of 38% four months later. Rabbit No. 9 showed a weight loss of 4.8% at the end of exposure, and 44.3% after 2 months. These phenomena were also observed in other rabbits. This may be related to an aftereffect of chlorine.

Kalf-Kalif [9] states that the effect of chlorine in chronic intoxication endures for a long time after the cessation of the direct action of the poison.

In rabbits No. 8, 19, 5, 1, 7, 9, the first weight loss was observed in the first month of exposure, after which the body weight increased again. A lasting weight loss appeared only in the second or third month of poisoning. In other rabbits, the first weight drop was observed only after some three months of poisoning, after which the weight increased again, and fell off only in the seventh,

eighth, and ninth month of poisoning. In some rabbits, a significant weight loss occurred only after the cessation of exposure (after 1 – 2 months).

During pregnancy, neither a change nor a loss of weight occurred. All the rabbits showed a weight gain in the last 10 - 15 days.

The rabbits exhibited a reaction to the poisoning even after the first experiment. Most often, we saw sneezing during and after the experiment. Less often, we could see the rabbits scratch their noses. Somewhat later we found labored respiration during the experiment. This phenomenon was more frequent during the last exposures. Some rabbits exhibited slight excitation states during the first experiments. Two rabbits reacted with brain phenomena, showing severe excitation states in the last tests. We saw diarrhea in three rabbits, salivation in two, and lacrimation in one. The symptoms did not become worse during pregnancy. Only with rabbit No. 3 did convulsions occur during pregnancy (before delivery, before the last two experiments).

Figure 2. Telangiectatic expansion of bronchial blood vessels after chronic poisoning in the course of 1 year 5 months. (Experimental rabbit No. 3).

In the fourth, fifth, and sixth months of poisoning, some rabbits showed a weakening of the reaction to poisoning. Perhaps this can be explained by adaptation of the rabbits to chlorine.

Most rabbits showed changes in the respiratory organs on autopsy and histological examination. These could be linked to a chronic chlorine poisoning (Table 1).

TABLE 1. BODY WEIGHT CHANGES AND PATHOMORPHOLOGIC CHANGES IN THE RESPIRATORY ORGANS AFTER EXPERIMENTAL CHRONIC POISONING OF RABBITS WITH CHLORINE.

Rabbit No.	Weight before exposure	Body weight at end of exposure	Body weight at end of observation	Change of weight at end of exposure	Change of weight at end of observation	Duration of exposure	Duration of observation	Number of Experiments
20	2520	2400	2200	– 3.9	– 12.7	10 days	56 days	5
8	2290	1580	1450	– 31.0	– 36.6	1 mo.	1 mo. 7 days	12
19	2250	2070	1770	– 11.1	– 21.3	1 mo. 12 days	3 mo.	11
5	2805	2350	2300	– 16.2	– 18.0	1 mo. 27 days	2 mo. 5 days	23
1	2920	2300	–	– 17.8	–	2 mo. 27 days	3 mo. 4 days	36
9	2470	2350	1370	– 4.8	– 44.5	4 mo. 10 days	6 mo. 27 days	41
7	2660	1550	1400	– 43.6	– 47.8	4 mo. 8 days	4 mo. 17 days	51
18	2375	1700	1520	– 37.0	– 44.7	4 mo. 8 days	5 mo.	54
6	2750	2680	2700	– 2.5	– 1.8	6 mo. 6 days	9 mo. 22 days	68
4	3020	2620	1870	– 13.2	– 38.0	6 mo. 6 days	9 mo. 15 days	69
11	2500	Control Animal	2720	–	+ 8.8	–	–	–
21	2700	2570	2370	– 4.8	– 12.2	6 mo. 21 days	12 mo. 30 days	73
22	2300	2120	1950	– 10.0	– 15.2	6 mo. 21 days	11 mo. 27 days	72
15	2750	2750	2650	–	– 3.6	6 mo. 27 days	11 mo. 25 days	7

TABLE 1. BODY WEIGHT CHANGES AND PATHOMORPHOLOGIC CHANGES IN THE RESPIRATORY ORGANS AFTER EXPERIMENTAL CHRONIC POISONING OF RABBITS WITH CHLORINE.

Outcome of experiment	Pathological findings in the Respiratory Organs
Terminated because of catarrh	
Died on day of last experiment	Catarrhalic secretion in the bronchi with partial alveolar atelectasis. Slight diffuse infiltration of the bronchial walls.
Died after 27 days following the last experiment	Moderate infiltration of bronchial submucosa.
Died after 2 days following the last experiment	Pleuropneumonia; atelectasis, catarrhalic confluent pneumonia with centers of aputrid necrosis and suppurative decay; fibrinous-suppurative pleuritis
Died after 3 days following the last experiment	Atrophy of the bronchial mucous membrane and infiltration of the submucosa. Venous hyperemia. Infiltration of the bronchial submucosa; vacuolozation of alveolar epithelial cells.
Died 2 months after the last experiment	Catarrhalic bronchitis. Extravasation into the bronchial lumina, atelectasis, emphysema (Macerated fetus).
Died after 3 days following the last experiment	Extensive extravasation; blood in alveoli, bronchial lumina, and submucosa. Emphysema in some parts of the lung. Atelectasis in the hemorrhagic portions.
Died after 2 days following the last experiment	Hyperemia and moderate infiltration of bronchial mucous membrane. Hyperemia and significant anthracosis of lungs. In the fine bronchia, local metaplasia of epithelia to many-layered plate epithelia.
Died 3 months after the last experiment	Catarrhalic bronchitis, extensive atelectases. Degeneration of alveolar epithelial cells. Extravasation into the lung tissue. Brown pigment in alveolar cells, fibrinous-suppurative pleuritis.

TABLE 1. BODY WEIGHT CHANGES AND PATHOMORPHOLOGIC CHANGES IN THE RESPIRATORY ORGANS AFTER EXPERIMENTAL CHRONIC POISONING OF RABBITS WITH CHLORINE.

Rabbit No.	Weight before exposure	Body weight at end of exposure	Body weight at end of observation	Change of weight at end of exposure	Change of weight at end of observation	Duration of exposure	Duration of observation	Number of experiments
17	2670	2720	2440	− 5,2	− 14.9	7 mo. 2 days	11 mo. 26 days	81
2	2780	2100	1950	− 24,4	− 29,8	9 mo. 10 days	9 mo. 17 days	111
3	2300	2170	1450	− 19,5	− 36,9	1 yr. 5 mo.	1 yr. 4 mo.	113

TABLE 1. BODY WEIGHT CHANGES AND PATHOMORPHOLOGIC CHANGES IN THE RESPIRATORY ORGANS AFTER EXPERIMENTAL CHRONIC POISONING OF RABBITS WITH CHLORINE.

Outcome of experiment	Pathological findings in the Respiratory Organs
Died 4 months after the last experiment	Confluent catarrhalic, hemorrhagic broncho-pneumonia (abscessed in places). Very much exudate in the alveoli and bronchioles. The inflammation is of desquamative character in places. Some alveoli are completely filled with alveolar epithelial cells (cells partially degenerated).
Killed	
Killed by electricity 4½ months after the last experiment	Hyperemia of the bronchial mucous membrane (four encapsulated fetuses in a common capsule in the abdomen at the left margin of the stomach).
Killed by electricity 4½ months after the last experiment	Very many epitheloid-lymphoid nodules in the vicinity of pigment collections in the lungs. Stases and induration of the lungs. Metaplasia of the bronchial epithelial cells with desquamation of the cells. Some parts with central necrosis. Blood in the bronchi.
Killed by electricity 3½ months after the last experiment	Swelling of the alveolar epithelia.
Killed by electricity 5 months after the last experiment	Hemorrhagic centers in alveoli and bronchi. Suppurative-necrotic bronchitis. Bronchial lumina full of suppurative-necrotic mass.
Died 4 days after the last experiment	Leucocytic infiltration of bronchial submucosa. Inflammatory infiltration of the bronchial submucosa. Atelectatic centers with proliferation of interstitial tissue.
Died 2 months after the last experiment	Angiomatosis of bronchial submucosa (large cavernous spaces full of blood). Mucous membrane catarrh. Hemorrhages into the bronchial lumen. Focal hemorrhagic pneumonia.

For illustration, we can introduce one series of autopsy protocols, No. 9, 19, 5, 1, 9, etc. Thus, for example, in rabbit No. 7 (51 exposures) we found extensive hemorrhagic centers in the respiratory organs, blood in the alveoli, in the bronchial lumina and submucosa, emphysema in some parts of the lungs, and atelectasis in the hemorrhagic parts. We found the same pathomorphologic picture in most of the poisoned rabbits. With rabbit No. 18 we found, here and there in the fine bronchi, metaplasia of the cylindrical epithelium into many-layered pavement epithelium.

The fact that we found the same picture of chronic catarrh also in rabbits which died spontaneously, or which were killed only after 2 - 5 months after the end of exposure is particularly important. (See Table 1: data for rabbits No. 9, 6, 4, 22, 17, and 3; also Figures 2 and 3.

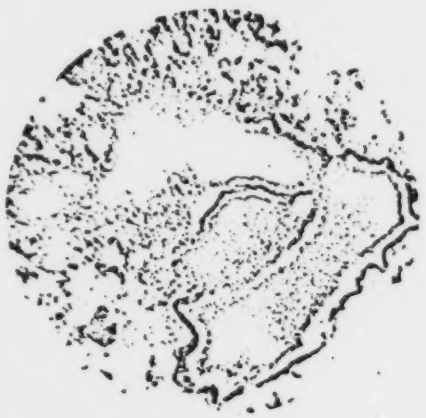

Figure 3. Catarrhal broncho-pneumonia after chronic poisoning over the course of 1 year and 5 months (experimental rabbit No. 3).

Such a long existence of the changes in the respiratory tract caused by the chronic action of small chlorine concentrations argues for the stability of these changes and for the high effectiveness of even these slight concentrations. The sex organs of the poisoned rabbits showed no pathological changes. In several rabbits (both control and experimental animals) we found spontaneous pathological disorders characteristic for these animals in various organs (most frequently in the brain) in the form of granulomas (often with cheesy necrosis) and perivascular infiltrations. In the liver they were in the form of nodules with necrotic caseations and in the form of diffuse cirrhosis [27, 28].

We could assume a general chlorine action in the sense of degenerative changes of the internal organs, in rabbit No. 9, for instance; but we were unable to provide a strict proof of this because there was an accompanying infectious disease.

The frequency of the infectious processes in the respiratory organs may be related to the fact that chlorine diminishes the bactericidal properties of these organs (Ronzani [20]), or that chlorine has a sensitizing action on the respiratory tract in relation to infection. We found hemosiderosis of the spleen more frequently in chlorine-exposed rabbits than in the control animals.

From 6 chlorine-exposed rabbits we obtained 24 individual offspring, and only 2 from the control rabbits. The offspring of our experimental animals were observed by the veterinary, Dr. Metjolkin, who consulted with us as necessary. Dr. Metjolkin studied the offspring of our chlorine-exposed rabbits and the state of their health. He found their development and body weight entirely satisfactory. The dynamics of the body weight in these offspring showed very great individual deviations from the average, due to individual variations. Up to $2\frac{1}{2}$ months, the weight of the offspring of the control female No. 11 was somewhat higher than the body weight of the offspring of the chlorine-exposed females. Beyond three months, the body weight of the offspring of control rabbit No. 11 was retarded, apparently due to a sickness. With respect to the offspring of the chlorine-exposed females, the offspring of females No. 2 and 22 gave the highest weight curves. The corresponding curves for the offspring of females No. 3, 15, and 21 were somewhat lower. It must be stressed that the body weight of the offspring of all the chlorine-exposed rabbits increased continuously for 7 - 8 months. Only in the offspring of females No. 3, 15, and 21 did the body weight remain below normal limits for the first 6 months. From 7 months on, the weights of the offspring of all the chlorine-exposed rabbits caught up. (See Tables 2 and 3 with the average weights of the offspring of the chlorine-exposed and control rabbits.)

Paralyses of the extremities were observed for three offspring of female No. 2 and 2 offspring of female No. 22 at the age of 4 3/4 and 6½ months. Two of these rabbits died. The other three recovered and were sacrificed some time later. Autopsies of all five of these young rabbits in which we had observed paralyses showed spontaneous parasitic processes which were also seen in some females. Obviously, the paralyses of the extremities were the result of spontaneous parasitic encephalitises.

TABLE 2. AVERAGE BODY WEIGHT OF THE OFFSPRING OF CHLORINE-EXPOSED RABBITS.

Age of animal	Offspring of female number:					
	2	22	15	21	3	11
						Control animal
12 Days	140,0	158.7	143,0	89,1	111,0	165,0
1 Month	371.7	345.0	360,0	242.5	256.0	495,0
2 Months	834.2	807.5	620,0	514.0	450,0	1065,0
3 "	1207,5	1137.5	850.0	754.0	540.0	1155,0
4 "	1437,5	1142.5	1100,0	852.0	748,3	1155,0
5 "	1635,0	1276,6	1163,0	964.0	920,0	–
6 "	1892.0	1506,0	1326,6	1214.0	–	–
7 "	1690,0	1640.0	1506,0	1368.0	1313,3	–
8 "	1963,0	1730,0	1576,6	1428,0	–	–
9 "	1903,3	–	–	–	–	–
10 "	–	–	–	–	–	–
11 "	1876	–	1985,0	1572,5	–	–
12 "	1970,0	–	–	–	–	–
13 "	2085,0	–	–	–	–	–
14 "	–	–	–	–	–	–
15 "	2250,0	–	–	–	–	–

Two occurrences of colic were observed in one offspring of female No. 3. This rabbit died at the age of 1½ months. Autopsy and microscopic investigation showed an acute catarrhalic intestinal

TABLE 3. BODY WEIGHT OF THE OFFSPRING OF CHLORINE-EXPOSED RABBITS

Age of animal	Offspring of exposed rabbits		Offspring of control animal	
	Average weight	Index	Average weight	Index
1 Month	335	100	495	100
2 Months	630	187	1065	215
3 "	900	268	1155	238
4 "	1035	308	1155	238
5 "	1184	352	–	–
6 "	1564	466	–	–
7 "	1479	440	–	–
8 "	1622	483	–	–
11 "	1700	506	–	–

process. Both offspring of the control female died at the age of $3\frac{1}{2}$ months. One of these rabbits had a convulsion. Autopsy showed pneumonia and myocarditis. Of the 24 offspring of chlorine-exposed females, a total of 8 rabbits died at ages of $1\frac{1}{2}$ - $7\frac{1}{2}$ months. The literature data indicate that we can consider such mortality figures at this age as within the normal range.

Analysis of the data cited leads to the following conclusions:

1. 15 rabbits were subjected to chronic poisoning with low chlorine concentrations (0.002 - 0.005 mg Cl_2 per liter air) for 1 - 9 months. In most of the experimental animals, we observed significant weight losses and disorders of the respiratory organs which are characteristic of the action of chlorine: catarrhalic changes of the upper respiratory tract, frequent metaplasia of the cylindrical epithelia of the bronchia into pavement epithelia, extensive centers of hemorrhages in the bronchi and lungs, lung emphysema and atelectases, and frequent infections diseases of the respiratory organs – pneumonias and pleuritises.

2. The disorders of the respiratory tract characteristic for the action of chlorine (at low concentration) proved to be stable, inasmuch as they were still present even after 2 - 5 months after the termination of exposure.

3. The frequency of infections diseases of the respiratory organs can be explained by assuming a sensitizing effect of chlorine on the respiratory tract, in respect to infection.

4. We found hemosiderosis of the spleen more often in the chlorine-exposed than in the control animals. We could relate this, hypothetically, to the hemolytic action of chlorine.

5. In isolated cases (e. g., in rabbit No. 9) we could conjecture that there was a general action of chlorine in the sense of degenerative or inflammatory changes; but we could not demonstrate it strictly in view of an accompanying infectious disease.

6. Six chlorine-exposed rabbits showed a normal course of pregnancy and birth. The lactation period also took a normal course in these rabbits.

7. Changes of the sex organs could not be detected in the chlorine-exposed rabbits.

8. Our chlorine-exposed rabbits gave healthy, well-developed offspring with satisfactory body weights.

9. The fact that macerated fetuses were found in two cases in the abdomens of the chlorine-exposed rabbits dictates, in view of the relative rareness of this phenomenon in "normal" animals, the careful recording of similar phenomena (macerated fetuses) in women working in chlorine plants, inasmuch as there is a related case of human pathology *.

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* See the investigation of R. M. Skljanskaja, L. M. Klaus and L. M. Ssidorowa: On the effect of chlorine on the female organism.

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